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Health Effects Assessment for Trihalogenated Methanes

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with selected trihalogenated methanes. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1985. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Halomethanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-051. NTIS PB81-117624.

U.S. EPA. 1982. Errata for Ambient Water Quality Criteria Document for Halomethanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC.

U.S. EPA. 1983a. Reportable Quantity Document for Chlorodibromomethane (Dibromochloromethane). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1983b. Reportable Quantity Document for Tribromomethane (Bromoform). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985. Health and Environmental Effects Profile for Bromochloromethanes. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a,b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

In this document, quantitative risk assessments for three trihalomethanes are reported. Only oral data were used in these assessments because the inhalation data were considered inadequate. A 90-day drinking water study in rats defined a NOAEL of 50 ppm (5.6 mg/kg/day) for bromoform (Chu et al., 1982b). Higher doses caused an increased incidence and intensity of liver lesions. Using these data, RfD_{SO} and RfD_{O} values of 0.056 and 0.0056 mg/kg/day (4.0 and 0.4 mg/day for a 70 kg human), respectively, were calculated for bromoform.

All three trihalomethanes have been tested for carcinogenicity by the National Toxicology Program, but only the results of the bromodichloromethane and chlorodibromomethane studies are available. The chlorodibromomethane study (NTP, 1985) provided no evidence of carcinogenicity in F344/N rats, equivocal evidence of carcinogenicity in male B6C3F1 mice, and some evidence of carcinogenicity in female B6C3F1 mice. The data determined to be most appropriate for risk assessment were those that showed a significant dose-related increase in combined incidences of hepatocellular carcinomas or adenomas in female mice. These data were used to calculate a human q_1^* of 8.4×10^{-2} $(mg/kg/day)^{-1}$ for chlorodibromomethane.

The results of the bromodichloromethane bioassay were available only as a board draft report (NTP, 1986a), but the data provided "clear evidence" of the carcinogenicity of this compound in rats and mice. Statistically significant increases in tumor incidence occurred for tumors of the large intestine and kidneys in both sexes of F344/N rats, for kidney tumors in male B6C3F1 mice, and liver tumors in female mice. NTP (1986a) noted that the tumors of the large intestine and kidney are uncommon in these strains of rats and mice. The data for combined incidence of hepatocellular adenomas or carcinomas in female mice were selected to calculate a human q_1^* of 1.3×10^{-1} $(mg/kg/day)^{-1}$ for bromodichloromethane.

Because bromodichloromethane and chlorodibromomethane have been found to be carcinogenic, and because bromoform has given positive results in mutagenicity assays, the toxicity-based RfD_{SO} and RfD_{O} values for bromoform should be considered provisional pending release of the results from the NTP (1986b) bromoform bioassay.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BUN	Blood urea nitrogen
CAS	Chemical Abstract Service
CS	Composite score
DMBA	Dimethyl benzanthracene
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected physical and chemical properties and environmental fates of bromodichloromethane, chlorodibromomethane and bromoform are presented in Table 1-1.

Although the atmospheric half-lives of these chemicals resulting from their reactions with HO radical are not known, they are expected to be <2 years, based on the half-lives of structurally similar halomethanes (Lyman et al., 1982). Such long half-lives indicate that significant transport of these chemicals from troposphere to stratosphere will occur. Aquatic half-lives for bromodichloromethane, chlorodibromomethane and bromoform are the estimated volatilization half-lives based on published oxygen reaeration values. The half-lives in lakes and ponds are expected to be shorter with other removal processes such as photolysis, biodegradation and oxidation contributing to the loss of these compounds (Tabak et al., 1981; Kaczmar et al., 1984; Francois et al., 1979).

Based on the measured Henry's Law constant as well as the vapor pressures listed, volatilization from both wet and dry soil surfaces should be relatively rapid.

TABLE 1-1

Selected Physical and Chemical Properties and Half-lives for Trihalomethanes

Property	Bromodichloromethane	Chlorodibromomethane	Bromoform
CAS number:	75-27-4	124-48-1	75-25-2
Chemical class:	halogenated aliphatic hydrocarbon	halogenated aliphatic hydrocarbon	halogenated aliphatic hydrocarbon
Molecular weight:	163.83	208.31	252.77
Molecular formula:			
Melting point (°C):	-57.1[a]	NA	7.5[a]
Boiling point (°C):	90[a]	119[a]	149-150[a]
Vapor pressure:	50 mm Hg at 20°C[b]	15 mm Hg at 10°C[b]	5.6 mm Hg at 25°C[c]
Water solubility:	3032 mg/ℓ at 30°C[d]	1050 mg/ℓ at 30°C[d]	3033 mg/ℓ at 25°C[c]
Log octanol/water partition coefficient:	1.88[b] (calculated)	2.09[b] (calculated)	2.03[b] (calculated)
Bioconcentration factor:	16[e] (calculated)	25[e] (calculated)	7[f] (calculated)

TABLE 1-1 (cont.)

Property	Bromodichloromethane	Chlorodibromomethane	Bromoform
Henry's Law constant:	1.5×10^{-3} m³·atm/mol at 20°C[g]	8.1×10^{-4} m³·atm/mol at 20°C[g]	4.3×10^{-4} m³·atm/mol at 20°C[g]
Half-life in water:	33 minutes to 12 days[h] (rivers, streams)	43 minutes to 16.6 days[h] (rivers, streams)	63 minutes to 24.2 days[h] (rivers, streams)

[a]Weast, 1980

[b]Callahan et al., 1979

[c]Mackay and Shui, 1981

[d]McNally and Grob, 1983

[e]Using log BCF = log K_{ow} - 0.23 (Lyman et al., 1982)

[f]Using log BCF = 2.791-0.564 log S (Lyman et al., 1982)

[g]Nicholson et al., 1984

[h]Kaczmar et al., 1984

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2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

The U.S. EPA (1980a) reported that absorption of halomethanes can occur by the gastrointestinal tract, but no specific details concerning the three trihalomethanes in this document were provided. Smith et al. (1985) reported that gastrointestinal absorption of bromodichloromethane was "judged to be nearly complete" and fairly rapid in rhesus monkeys given an oral dose of 10 mg/kg ^{14}C-bromodichloromethane. Peak blood levels of radioactivity occurred at ~4 hours after treatment. Cumulative excretion from the feces accounted for only ~0.06-1.65% of the dose of radioactivity over a 24- to 72-hour period.

2.2. INHALATION

The U.S. EPA (1980a) reported that absorption of halomethanes by the lungs is "fairly efficient" and is of "primary importance" relative to gastrointestinal and dermal routes. No details concerning the trihalomethanes discussed in this report were provided.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Chu et al. (1982b) conducted a 90-day study in which groups of 20 male and 20 female Sprague-Dawley rats were exposed to 0, 5, 50, 500 or 2500 ppm of chlorodibromomethane, bromodichloromethane or bromoform in their drinking water. After the 90-day exposure, half of the animals in each group were sacrificed and the other half allowed to live for an additional 90-day recovery period. Bromodichloromethane caused decreased food consumption and weight gain at the highest dose level. Chlorodibromomethane and bromoform caused decreased food consumption and decreased lymphocyte counts at 2500 ppm. The highest levels that caused no adverse effects in this study were 5 ppm bromodichloromethane, 5 ppm chlorodibromomethane and 50 ppm bromoform. In all cases, higher doses caused mild histological effects, which were dose-related in incidence and intensity, in the liver and thyroid. These effects were reversible and were not apparent 90 days after the end of the exposure. As calculated by the U.S. EPA (1982) using data provided by the primary author, these drinking water concentrations correspond to male-female average doses of 0.56 mg/kg/day bromodichloromethane, 0.515 mg/kg/day chlorodibromomethane, and 5.6 mg/kg/day bromoform. As stated by the U.S. EPA (1982), an average value was used to estimate a more accurate animal NOAEL, since there were no major differences between sexes in sensitivity to these compounds.

Chu et al. (1982a) conducted similar studies of shorter duration with groups of 10 male SD rats exposed to 0, 5, 50 or 500 ppm of each trihalomethane in drinking water for 28 days. No effects in terms of growth, food intake, histopathology, serum biochemical parameters, and hepatic microsomal

enzyme activities were observed. A slight increase in relative kidney weight occurred in rats exposed to 500 ppm bromoform and 5 and 500 ppm bromodichloromethane.

The NTP (1985) conducted studies in which groups of 10 F344/N rats/sex and 10 B6C3F1 mice/sex received 0, 15, 30, 60, 125 or 250 mg/kg chlorodibromomethane by gavage in corn oil 5 days/week for 13 weeks. In rats, toxic effects occurred only in the high-dose group and included liver and kidney lesions and mortality of 9/10 rats of each sex. No treatment-related deaths occurred among the mice, but liver and kidney lesions were observed in high-dose males.

The NTP (1986a) conducted 14-day and 13-week studies with F344-N rats and B6C3F1 mice exposed to bromodichloromethane. In the 14-day studies, groups of five male and five female rats received oral doses of 38-600 mg/kg/day and equal numbers of mice 19-300 mg/kg/day. Decreased weight gain occurred in rats of both sexes at 300 and 600 mg/kg/day. All male mice receiving 150 and 300 mg/kg/day died. In the 13-week studies, groups of 10 rats/sex received oral doses of 19-300 mg/kg/day; groups of 10 male mice received 6.25-100 mg/kg/day; and groups of 10 female mice received 25-400 mg/kg/day. Terminal body weights of rats at 150 and 300 mg/kg/day were lower than vehicle controls. Histopathological changes in the liver occurred in rats at 300 mg/kg/day and female mice at 200 and 400 mg/kg/day. Degeneration and necrosis of the kidneys occurred in male mice at 100 mg/kg/day and male rats at 300 mg/kg/day.

EG and G (1980) conducted 13-week gavage studies using Fischer 344 rats and B6C3F1 mice (10/sex/species) given bromoform at dosages of 12-400 mg/kg/day. Body weight gain depression >10% occurred in male mice at $\geq$50 mg/kg/day and in female mice at all doses. Fatty metamorphosis occurred in

the livers of male mice at ≥200 mg/kg/day. Male rats had clear cell foci of the liver at doses of 12 mg/kg/day and above. No compound-related lesions were observed in females of either species.

Schuller et al. (1978) and Munson et al. (1978) studied the effects of the three trihalomethanes on humoral and cell-mediated immunity. These studies, however, were published only as abstracts and are difficult to evaluate. In both studies, male and female ICR mice were treated with gavage dosages of 0, 0.2-0.3, 12.5 or 125 mg/kg/day for 90 days. In the Schuller et al. (1978) study, no compound affected liver function, kidney function or hematological parameters. Bromodichloromethane at 125 mg/kg/day depressed delayed hypersensitivity in males and females. Chlorodibromomethane and bromoform had no such effect at any dosage. In the Munson et al. (1978) study, all three compounds caused a "dose-dependent" suppression of hepatic phagocytosis of Listeria monocytogenes in males and females. Chlorodibromomethane also inhibited splenic phagocytosis in the 12.5 and 125 mg/kg/day male mice.

In a 14-day gavage study (Condie et al., 1983), groups of 5-10 male CD-1 mice were exposed to bromodichloromethane (0, 37, 74 and 148 mg/kg/day), chlorodibromomethane (0, 37, 74 and 147 mg/kg/day), and bromoform (0, 72, 145 and 289 mg/kg/day). In the mice exposed to bromodichloromethane, kidney function was affected at 74 and 148 mg/kg/day. Clinical chemistry effects and histopathological effects on liver and kidneys also occurred at the highest dose. Similar effects occurred in the mice exposed to chlorodibromomethane, but only at the highest dose level. In the mice exposed to bromoform, effects on kidney function and histopathological effects on liver and kidneys occurred at the two highest doses. The highest NOAELs from these experiments were 37 mg/kg/day bromodichloromethane, 74 mg/kg/day chlorodibromomethane and 72 mg/kg/day bromoform.

Munson et al. (1982) conducted a study in which groups of 7-12 CD-1 mice of each sex were exposed to one of the three trihalomethanes by gavage for 14 days at dosages of 50, 125 or 250 mg/kg/day. Among the mice exposed to bromodichloromethane, high-dose mice experienced decreased body weight gain and effects on clinical chemistry (SGOT, SGPT, BUN and glucose), hematological parameters (fibrinogen) and the immune system. Middle- and high-dose mice both had significantly increased relative liver weights and decreased spleen weights (females only). There were no differences between low-dose mice (50 mg/kg/day) and controls in any of the parameters examined (body weights, organ weights, clinical chemistry, hematology and humoral immunity). High-dose mice exposed to chlorodibromomethane experienced decreased body weight gain, increased liver weights, decreased spleen weights, decreased fibrinogen concentrations, decreased serum glucose levels, increased SGOT and SGPT and effects on the immune system. Middle-dose mice also had increased relative liver weights and immune system effects. There were no differences between low-dose mice and controls in any of the parameters measured. Male mice exposed to bromoform experienced decreased body weight gain, increased liver weight, and hematological effects at the middle and high doses. High-dose males and females also experienced effects on clinical chemistry parameters and the immune response (males only). Once again, the 50 mg/kg/day dosage was a NOEL. Histological examinations of major organs were apparently not performed in this study.

Dunnick et al (1985) conducted a 13-week study in which male and female Fischer 344/N rats and B6C3F1 mice received gavage doses of 0, 15, 30, 60, 125 and 250 mg/kg/day of chlorodibromomethane. Unspecified hepatic and renal toxicity occurred in high-dose male and female rats and male mice. Mortality was increased in high-dose male and female rats.

Balster et al. (1979) reported negative results in behavioral studies with groups of eight mice receiving gavage doses of trihalomethanes for 14 or 90 days. Swimming behavior was unaffected by doses of 1.2 or 11.6 mg/kg/day bromodichloromethane, 1.0 or 10.0 mg/kg/day chlorodibromomethane and 0.9 or 9.2 mg/kg/day bromoform administered for 14 days. No motor impairment was evident at these dosages when they were administered for 90 days. Dosages of 100 mg/kg/day of each trihalomethane administered for 30 days had no effect on a passive avoidance learning task. Balster and Borzelleca (1982) found that operant behavior of mice was affected at 100 and 400 mg/kg/day bromodichloromethane and bromoform and at 400 mg/kg/day chlorodibromomethane in a 60-day gavage study. The lowest dose tested was 10 mg/kg/day.

3.1.2. Inhalation. There is relatively little information concerning the toxicity of these three trihalomethanes by the inhalation route. Dykan (1962) reported that rats exposed to 25 ppm bromoform 4 hours/day for 2 months experienced effects on liver glycogenolysis and prothrombin synthesis.

3.2. CHRONIC

3.2.1. Oral. NTP (1985) and Dunnick et al. (1985) reported results of an oral chronic toxicity/carcinogenicity study of chlorodibromomethane using rats and mice. In this study, groups of Fischer 344/N rats and B6C3F1 mice (50/sex/species) received doses of 0, 40 or 80 mg/kg/day (rats) or 0, 50 or 100 mg/kg/day (mice) by gavage in corn oil for 104 weeks. Fatty change and cytoplasmic changes occurred in the livers of treated male and female rats. High-dose male rats also experienced decreased body weight gains. In the mouse study, high-dose males had reduced survival relative to controls. Treated males and high-dose females had reduced body weight gains. Treated males had necrosis and hepatocytomegaly of the liver and nephrosis of the

kidney. Treated females also had calcification and fatty changes in the liver. Results of this study pertaining to possible carcinogenicity of chlorodibromomethane are presented in Section 4.2.1.

NTP (1986a) treated groups of 50 rats/sex and 50 mice/sex with bromodichloromethane in corn oil by gavage for 102 weeks: rats received 0, 50 or 100 mg/kg; male mice received 0, 25 or 50 mg/kg; female mice received 0, 75 or 150 mg/kg, 5 days/week. No compound-related clinical signs were observed in treated rats, but final body weights of high-dose males were 88% and high-dose females were 79% of those of vehicle controls. There appeared to be no effect on survival. The most significant nonneoplastic lesions were the presence of cytomegaly of the tubular epithelial cells of the kidney, a slightly increased incidence of liver necrosis in both treated groups of male rats and an increased incidence of fatty liver infiltration in treated rats of both sexes. No compound-related signs of toxicity were observed in treated mice, but high-dose females had final body weights 75% of those of vehicle controls. No effects on body weight were observed in males or low-dose females. Survival of male mice was not affected by treatment, but both treated groups of females had survival significantly less than that of vehicle controls, which was attributed primarily to the development of ovarian abcesses. Both treated groups of male mice had cytomegaly of renal tubular cells, an increased incidence of fatty changes of the liver and high-dose male mice had an increased incidence of focal atrophy of the testicular tubules. An increased incidence of ovarian abcesses was observed in both treated groups of female mice. Neoplastic lesions are discussed in Section 4.2.

3.2.2. Inhalation. Chronic inhalation studies could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Possible teratogenicity of the three trihalomethanes was investigated by Ruddick et al. (1983) who administered gavage doses of 0, 50, 100 or 200 mg/kg/day of each compound in corn oil to groups of 9-15 pregnant SD rats on days 6-15 of gestation. No treatment-related teratogenic effects occurred in any group. Bromodichloromethane and chlorodibromomethane caused maternal toxicity (reduced weight gain) at the highest dosage. Bromodichloromethane also caused increased relative kidney and brain weights at the highest dosage. Bromoform did not cause any maternal toxicity. Bromodichloromethane and bromoform appeared to cause some fetotoxicity as determined by the incidence of sternebred aberrations in all groups of treated rats relative to controls. There was no treatment-related fetotoxicity in chlorodibromomethane-treated rats.

Borzelleca and Carchman (1982) conducted a multi-generation study in which groups of 10 male and 30 female ICR mice were exposed to chlorodibromomethane in emulphor (a polyoxyethylated nonionic surfactant) (U.S. EPA, 1985) at bromomethane concentrations of 0, 0.1, 1.0 or 4.0 mg/mℓ in drinking water. The mice were 9 weeks old at the beginning of the treatment, which was continuous throughout the experiment. After 35 days of exposure, animals were mated to produce the F_{1a} generation; subsequent matings of F_0 mice produced the F_{1b} and F_{1c} generations. The F_{1b} offspring were exposed to the same chlorodibromomethane concentrations in drinking water for 11 weeks beginning after weaning at 3 weeks of age, and then were mated to produce the F_{2a} generation. High-dose F_0 mice experienced gross liver pathology and decreased terminal body weights. Litter size, gestation index, pup viability and survival of the F_1 generation were significantly reduced in the high-dose mice. According to the authors, the

"nominal" chlorodibromomethane dosage at this level was 685 mg/kg/day. At 1 mg/mL in the drinking water, terminal body weights of females were reduced, and gross liver pathology was evident in 70% of the F_0 mice. In certain generations, there were significant decreases in litter size, pup viability, postnatal body weight and lactation index at 1 mg/mL. The only effects observed at 0.1 mg/mL were decreased postnatal body weights in the F_{2b} generation, which remained significantly reduced at 21 days after birth. Adult mice of the F_0 and F_{1b} generations had gross liver lesions characterized by yellow color, presumably caused by fat accumulation. No treatment-related teratogenic effects were reported at any dose level.

3.3.2. Inhalation. Data concerning teratogenicity or reproductive effects of the three trihalomethanes by inhalation exposure could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Several studies concerning possible potentiation of trihalomethane toxicity by chlordecone have been published. Unlike chloroform, the toxicity of bromoform does not appear to be potentiated by chlordecone pretreatment. Agarwal and Mehendale (1983) fed male Sprague-Dawley rats diets containing 0 or 10 ppm chlordecone for 14 days, followed by an intraperitoneal injection of 25-300 µL/kg bromoform on the 15th day. No significant differences in hepatotoxic effects (histopathology or serum enzyme activities) were observed between the two groups. Klingensmith and Mehendale (1981) also reported that chlordecone or phenobarbitol pretreatment had no effect on the toxicity of an intraperitoneal dose of 10 µL/kg bromoform in rats. On the other hand, hepatotoxicity of bromodichloromethane and chlorodibromomethane is apparently greatly enhanced by chlordecone pretreatment. Plaa and Hewitt (1982) conducted a study in which groups of male rats were

treated with a gavage dose of vehicle or 50 mg/kg chlordecone 18 hours before receiving gavage doses of 0.1 or 0.5 mL/kg of bromoform, bromodichloromethane or chlorodibromomethane. Hepatotoxicity of bromodichloromethane and chlorodibromomethane was greatly enhanced by chlordecone, but hepatotoxicity of bromoform was unaffected.

Toxicity of bromodichloromethane and chlorodibromomethane was also enhanced by acetone. Hewitt et al. (1983) treated male SD rats with gavage doses of 15 mmol/kg acetone 18 hours before receiving gavage doses of 0.25-1.00 mL/kg bromodichloromethane or chlorodibromomethane. The acetone pretreatment significantly increased the hepatotoxicity of these compounds.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. U.S. EPA (1980a) evaluated several epidemiological studies concerning the possible association between trihalomethane levels in drinking water and cancer incidence among the U.S. population. U.S. EPA (1980a) concluded that the positive correlation between drinking water quality and cancer mortality might be due to the presence of trihalomethanes. Cantor et al. (1978) reported positive correlations between cancer mortality rates and levels of brominated trihalomethanes (mostly bromodichloromethane and chlorodibromomethane, but also bromoform) in drinking water.

Aldrich and Peoples (1982) examined the possible association of a high level of malignant melanoma in Brevard County, Florida with levels of trihalomethanes in the drinking water. The county was divided into three regions having low, median and high levels of trihalomethanes. Chloroform and bromodichloromethane were the major water contaminants with lesser amounts of dibromochloromethane and still lesser amounts of bromoform. The survey of melanoma cases showed a relationship between observed new cases of melanoma (between 1975 and 1977) and levels of trihalomethanes in the water. Although there was some association between the levels of the bromochloromethanes and melanoma, chloroform was related in a dose-related manner. Levels of chloroform in the water were also higher than either bromochloromethane compound. Two other factors cannot be ignored, age and sunlight. The entire population of Brevard County is older (retirees) and inclined to outdoor activities. However, taking these factors into account, the above data suggests a relationship between increased cancer risk and trihalomethanes.

Using cancer incidence data for the state of Iowa, Isacson et al. (1983) attempted to correlate the source of drinking water and its trihalomethane contaminants with specific types of cancer. Levels of chloroform, bromodichloromethane and dibromochloromethane ranged from 0-900, 0-220 and 0-17.0 µg/ℓ, respectively. When cancer cases were categorized as to the levels of each contaminant in their drinking water, a slight dose-related increase in the incidence of bladder cancer in males, lung cancer in males, and rectal cancer in both sexes was noted for bromodichloromethane. The incidence of bladder cancer in males, breast cancer in females, and stomach cancer in males was elevated in a dose-related manner when categorized by dibromochloromethane exposure. The significance of these increased cancer incidences relative to exposure levels of the bromochloroethanes was not discussed. In most cases, the incidence of cancers of a specific type were only slightly elevated in the high exposure group compared with the low exposure group. The authors (Isacson et al., 1983) proposed that these data do suggest an association between the level of trihalomethanes (including chloroform) in drinking water and bladder cancer in males, lung cancer in females and rectal cancer in both species.

4.1.2. Inhalation. Data concerning carcinogenicity of the three trihalomethanes to humans by inhalation exposure could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. NTP (1985) conducted a 2-year carcinogenicity bioassay with chlorodibromomethane in rats and mice. Groups of 50 male and 50 female F344/N rats received gavage doses of 0, 40 or 80 mg/kg in corn oil 5 days/week for 104 weeks. Groups of 50 male and 50 female B6C3F1 mice received gavage doses of 0, 50 or 100 mg/kg in corn oil 5 days/week for 105 weeks.

An overdose of chemical was given to low-dose mice of both sexes at week 58, which resulted in the deaths of 35 males, making the size of this group inadequate for analysis of neoplasms. Low-dose female mice were apparently unaffected. Chlorodibromomethane treatment significantly increased the incidence of hepatocellular adenomas (control 2/50, low-dose 4/49, high-dose 11/50) and the combined incidences of hepatocellular adenomas or carcinomas (control 6/50, low-dose 10/49 and high-dose 19/50) in high-dose female mice as determined by the Fisher Exact test (p=0.002). There was also a significant dose-related trend in combined incidences of hepatocellular adenomas or carcinomas in female mice as determined by the Cochran-Armitage trend test (p=0.002). In high-dose male mice, the incidence of hepatocellular carcinomas was significantly increased (control 10/50 and high-dose 19/50), but the combined incidence of hepatocellular adenomas or carcinomas (control 23/50 and high-dose 27/50) was marginally significant by the life table test but not by the incidental tumor test. NTP (1985) concluded that, under the conditions of these studies, there was no evidence of carcinogenicity in male or female F344/N rats. There was "equivocal evidence of carcinogenicity" in male B6C3F1 mice.

A chronic toxicity/carcinogenicity study of bromodichloromethane using F344/N rats and B6C3F1 mice was conducted by NTP (1986a). This study was available as a draft report and had not yet been completely reviewed. In this study, groups of 50 male and 50 female rats received gavage doses of 0, 50 or 100 mg/kg/day in corn oil 5 days/week for 102 weeks. Groups of 50 male mice received 0, 25 or 50 mg/kg/day and groups of 50 female mice received 0, 75 or 150 mg/kg/day according to the same schedule. The study using male rats was restarted at 10.5 months into the original study because a temperature elevation killed most of the vehicle control male rats.

Survival of treated rats was comparable with vehicle controls, but mean body weights of high-dose rats were decreased during the last 1.5 years of the study. Body weights of high-dose female mice were decreased during the last 1.5 years of the study, but no other significant treatment-related effects on survival or body weight occurred in mice. A variety of treatment-related nonneoplastic lesions were observed in treated mice and rats, with liver and kidneys being the primary target organs. Bromodichloromethane caused statistically significant dose-related increases in incidences of neoplasms of the large intestine and kidneys in male and female rats, the kidneys in male mice and the liver in female mice. The incidence data and statistical test results are presented in Tables 4-1 and 4-2. According to NTP (1986a), the neoplasms of the large intestine and kidneys are uncommon tumors in these strains of rats and mice. The NTP (1986a) concluded that these studies provided "clear evidence of carcinogenic activity" of bromodichloromethane in F344/N rats and B6C3F1 mice.

The National Toxicology Program is also conducting carcinogenicity bioassays with bromoform (NTP, 1986b). The chronic pathology working group for the bromoform study is in progress.

4.2.2. Inhalation. Data concerning carcinogenicity bioassays of trihalomethanes by inhalation exposure could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Theiss et al. (1977) examined production of lung adenomas in strain A mice following multiple intraperitoneal injections of various compounds. They reported that 18-24 injections of 4, 48 or 100 mg/kg bromoform resulted in a significantly higher number of lung adenomas per mouse relative to controls in the middle-dose group, but not the low- or high-dose groups.

TABLE 4-1

Compound-related Increased Incidences of Neoplasms in Rats in the 2-year Gavage Studies of Bromodichloromethane[a]

Neoplasms	Incidences		
	Vehicle Control[b]	50 mg/kg[c]	100 mg/kg[c]
MALE			
Large Intestine			
Adenomatous polyp	0/50 (p<0.001)	3/50 (p=0.121)	33/50 (p<0.001)
Adenocarcinoma	0/50 (p<0.001)	11/50 (p<0.001)	38/50 (p<0.001)
Adenomatous polyp or adenocarcinoma	0/50 (p<0.001)	13/50 (p<0.001)	45/50 (p<0.001)
Kidney			
Tubular cell adenoma	0/50 (p<0.06)	1/50 (NA)	3/50 (p=0.121)
Tubular cell adenocarcinoma	0/50 (p<0.001)	0/50 (NA)	10/50 (p<0.001)
Tubular cell adenoma or adenocarcinoma	0/50 (p<0.001)	1/50 (p=0.500)	13/50 (p<0.001)
FEMALE			
Large Intestine			
Adenomatous polyp	0/46 (p<0.02)	0/50 (NA)	6/47 (p<0.014)
Adenocarcinoma	0/46 (p<0.001)	0/50 (NA)	7/47 (p<0.007)
Adenomatous polyp or adenocarcinoma	0/46 (p<0.001)	0/50 (NA)	12/47 (p<0.001)

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TABLE 4-1 (cont.)

Neoplasms	Incidences		
	Vehicle Control[b]	50 mg/kg[c]	100 mg/kg[c]
	FEMALE (cont.)		
Kidney			
Tubular cell adenoma	0/50 (p<0.005)	1/50 (p=0.500)	6/50 (p=0.013)
Tubular cell adenocarcinoma	0/50 (p<0.001)	0/50 (NA)	9/50 (p<0.001)
Tubular cell adenoma or adenocarcinoma	0/50 (p<0.001)	1/50 (p=0.500)	15/50 (p<0.001)

[a]Source: NTP, 1986a

[b]Values in parentheses are p values associated with the Cochran-Armitage trend test

[c]Values in parentheses are p values from the Fischer exact test comparing tumor incidence rates of the dosed group with that of vehicle controls

NA = Not applicable

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TABLE 4-2

Compound-related Increased Incidences of Neoplasms in Mice in the 2-year Gavage Studies of Bromodichloromethane[a]

Neoplasms	Incidences		
	Vehicle Control[b]	50 mg/kg[c]	100 mg/kg[c]
MALE			
Kidney			
Tubular cell adenoma	1/49 (p=0.031)	2/50 (p=0.508)	6/50 (p=0.059)
Tubular cell adenocarcinoma	0/49 (p<0.015)	0/50 (NA)	4/50 (p<0.061)
Tubular cell adenoma or adenocarcinoma	1/49 (p<0.003)	2/50 (p=0.508)	9/50 (p<0.009)
FEMALE			
Liver			
Hepatocellular adenoma	1/50 (p<0.001)	13/48 (p<0.001)	23/50 (p<0.001)
Hepatocellular carcinoma	2/50 (p=0.009)	5/48 (p=0.201)	10/50 (p=0.014)
Hepatocellular adenoma or carcinoma	3/50 (p<0.001)	18/48 (p<0.001)	29/50 (p<0.001)

[a]Source: NTP, 1986a

[b]Values in parentheses are p values associated with the Cochran-Armitage trend test

[c]Values in parentheses are p values from the Fischer exact test comparing tumor incidence rates of the dosed group with that of vehicle controls

NA = Not available

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No significant results were obtained with mice receiving 18-24 injections of 20, 40 or 100 mg/kg bromodichloromethane.

The trihalomethanes have been tested for mutagenicity in the reverse mutation assay in Salmonella typhimurium, the dominant lethal test in male ICR mice and the sister chromatid exchange assay in mouse bone marrow cells and human lymphocytes. All three trihalomethanes were consistently positive in S. typhimurium strain TA100 without metabolic activation in a vapor phase test performed in a desiccator (Simmon et al., 1977). The intensity of the response was dose-related. Borzelleca and Carchman (1982) obtained negative results in a dominant lethal test in male mice from a multi-generation reproduction study; the mice were treated with chlorodibromomethane in drinking water at 0.1-4.0 mg/mℓ. All three halomethanes increased the frequency of sister chromatid exchanges in bone marrow cells in an in vivo test in ICR mice treated for 4 days with 25 or 50 mg/kg/day (Morimoto and Koizumi, 1983). There appeared to be no major differences between compounds in the magnitude of the positive response. In an in vitro test in human lymphocytes, all three compounds, in concentrations of 1.6×10^{-5} to 5×10^{-2} M, induced sister chromatid exchanges and bromoform gave the most positive response (Morimoto and Koizumi, 1983).

4.4. WEIGHT OF EVIDENCE

The available epidemiological data suggest a possible association between trihalomethane levels in drinking water and incidences of various types of cancer. Interpretation of these data is compromised, however, by the presence of chloroform, which is considered to be a probable human carcinogen. Therefore, the available data for evaluating the carcinogenic potential of the three trihalomethanes alone in humans are considered inadequate because of the confounding with chloroform.

NTP (1986a) conducted carcinogenicity bioassays with rats and mice exposed to bromodichloromethane. These experiments provided "clear evidence of carcinogenic activity" in both species. Bromodichloromethane caused increased incidences of tumors of the large intestine and kidney in male and female rats, kidney tumors in male mice, and liver tumors in female mice.

NTP (1985) conducted lifetime animal carcinogenicity bioassays in rats and mice with chlorodibromomethane. This study provided equivocal evidence of carcinogenicity in male mice (increased incidence of hepatocellular carcinomas in high-dose males) and some evidence of carcinogenicity in female mice (increased incidence of hepatocellular adenomas and increased combined incidence of hepatocellular adenomas or carcinomas). Additional data concerning bromoform will be provided by the National Toxicology Program bioassay in progress when it becomes available.

Trihalogenated methanes can be classified as follows:

Dichlorobromomethane: Cancer bioassay studies in rats and mice provide sufficient carcinogenic evidence in two species. Therefore, according to EPA carcinoen assessment guidelines, dichlorobromomethane could be placed in Group B2.

Monochlorodibromomethane: Cancer bioassay studies on monochlorodibromomethane in rats and mice provide a positive carcinogenic evidence in B6C3F1 mice (males and females). This carcinogenic evidence could be considered limited, and thereby monochlorodibromomethane can be placed in Group C according to EPA carcinogen assessment guidelines. However, monochlorodibromomethane is mutagenic and structurally similar to other known animal carcinogenic (dichlorobromomethane, chloroform, etc.) halomethanes. This auxiliary evidence provides us to elevate Group C carcinogen to Group B2 carcinogen to protect public health.

Tribromomethane: Cancer bioassays of tribromomethane in rats and mice are in progress. It is mutagenic. Its mutagenic action is considered to be stronger than other known animal carcinogens (dichlorobromomethane). Because of insufficient evidence tribromomethane at present can be classified in Group D. When the cancer bioassay data become available its classification will be re-evaluated.

5. REGULATORY STANDARDS AND CRITERIA

U.S. EPA (1980a) derived ambient water quality criteria for halomethanes as a group, including the three trihalomethanes that are the subject of this report, using the cancer-based criterion for chloroform. Although no suitable animal data were available for the three trihalomethanes at that time, U.S. EPA (1980a) concluded that the available epidemiological data and positive mutagenicity test results indicated that all of the halomethanes should be regulated as if they had the same carcinogenic potency as chloroform. Therefore, the criterion for total halomethanes associated with an individual lifetime cancer risk of 10^{-5} was the same as that for chloroform, 1.9 µg/ℓ.

In an update of the U.S. EPA (1980a) document, U.S. EPA (1982) recommended criteria for the three trihalomethanes based on toxicity rather than carcinogenicity. The RfD can be calculated from the 90-day study by Chu et al. (1982a). The 90-day NOAEL from this study can be divided by an uncertainty factor of 1000 to derive the RfD. The RfDs for bromodichloromethane, chlorodibromomethane and bromoform are 0.0005, 0.0006 and 0.006 mg/kg/day, respectively. These values were verified by the U.S. EPA (1986b,c,d). The corresponding recommended water quality criteria are 19, 18 and 190 µg/ℓ, respectively, based on daily consumption of 2 ℓ water and 6.5 g fish and shellfish (U.S. EPA, 1982).

ACGIH (1986) recommended a TLV of 0.5 ppm (5 mg/m³) for bromoform because of its irritant properties, its potential to cause liver damage and by analogy to related bromine compounds.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). The 90-day study by Chu et al. (1982b) provides the best basis for deriving RfD_{SO} values for bromoform. This study defined a NOAEL of 50 ppm bromoform in the drinking water. Higher doses caused an increase in incidence and intensity of liver lesions. Using body weight and water consumption data provided by the original authors, U.S. EPA (1982) determined that this NOAEL was equivalent to 5.6 mg/kg/day bromoform. This value was then divided by an uncertainty factor of 100 to account for interspecies extrapolation and intraspecies variations in sensitivity, resulting in an RfD_{SO} value of 0.056 mg/kg/day (4.0 mg/day for a 70 kg human) for bromoform. The selection of the Chu et al. (1982b) experiment as the basis for the derivation of the RfD_{SO} for bromoform ignores the observations by Schuller et al. (1978) and Munson et al. (1978) that a dose-dependent suppression of hepatic phagocytic activity occurred with this compound at doses as low as 0.2-0.3 mg/kg/day in a 90-day gavage study using mice. In these same experiments, however, no effects were observed on liver and kidney function or on hematological parameters. It is not certain that the suppressed hepatic phagocytosis reported has any biological significance. Since these experiments were only reported in abstract form, they can only be evaluated in a limited manner. No RfD_{SO}s are calculated for chlorodibromomethane and bromodichloromethane because of positive results in the NTP (1985, 1986a) carcinogenicity bioassays (Section 6.3.).

6.1.2. Inhalation (RfD_{SI}). The available data are insufficient for calculating RfD_{SI} values for any of the three trihalomethanes.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_0). There are no suitable chronic data available for bromoform. Therefore, data from the Chu et al. (1982b) study are also recommended for calculation of RfD_0 values for this compound. The calculations are performed as described in Section 6.1.1., except that an additional uncertainty factor of 10 is used to extrapolate from subchronic data to chronic exposure. The resulting RfD_0 values are 5.6 µg/kg/day (0.4 mg/day for a 70 kg human) for bromoform. This value is the same as the ADI calculated by U.S. EPA (1982).

U.S. EPA (1983a,b) calculated CS values for all three trihalomethanes, based on effects in rats and mice observed in various studies previously discussed in this document, and then selected those data that gave the maximum CS values to calculate RQs. No more recent data have been reported that would result in higher CS values. Therefore, only those studies that produced the maximum CS will be discussed here. In the case of bromoform, U.S. EPA (1983b) calculated an RQ based on an effective dose level of 12.5 mg/kg/day that caused suppression of hepatic phagocytosis in mice (Munson et al., 1978). In choosing this value, U.S. EPA (1983b) apparently assumed that the response at the lowest dose level, 0.3 mg/kg/day, was not significant. Using standard methodology, including an assumed mouse body weight of 0.03 kg, and dividing by an uncertainty factor of 10 to account for use of subchronic data, U.S. EPA (1983b) calculated a human MED of 6.6 mg/day and an RV_d value of 4.3. An RV_e of 6 was assigned; the resulting CS was 25.8.

No RfD_0 or CS values are calculated for chlorodibromomethane and bromodichloromethane because of positive results in the NTP (1985, 1986a) bioassay. Bromoform has also been tested by NTP (1986b). The chronic

pathology working group for the bromoform study is in progress. Because the closely related compounds chlorodibromomethane and bromodichloromethane were found to be carcinogenic, the toxicity-based RfD_{SO} and RfD_0 values for bromoform should be regarded as provisional until the carcinogenicity issue is resolved by the release of the NTP (1986b) results.

6.2.2. Inhalation (RfD_I). Data were inadequate to calculate RfD_I values for any of the three trihalomethanes.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The results of the NTP (1985) bioassay provide "some evidence of carcinogenicity" of chlorodibromomethane in female B6C3F1 mice. The combined incidences of hepatocellular adenomas or carcinomas was significantly increased in high-dose female mice, and there was a significant dose-related trend (vehicle control 6/50, low-dose 10/49 and high-dose 19/50). These data were used to calculate a q_1^* using the GLOBAL 82 multistage model (Howe and Crump, 1982) because they represented the only statistically significant increase in incidence of any malignant tumor. Data for female mice were chosen because the database for males in the NTP (1985) study was limited (i.e., there was only one treated group available for analysis of neoplasms). Using the data provided in Tables 6-1 and 6-2, an animal q_1^* of 6.7×10^{-3} $(mg/kg/day)^{-1}$ was computed, corresponding to a human q_1^* of 8.4×10^{-2} $(mg/kg/day)^{-1}$.

The NTP (1986a) bioassay provides "clear evidence" of the carcinogenicity of bromodichloromethane in rats and mice. Although this report has not yet been through peer review, it seems reasonable to perform a carcinogenicity-based risk assessment for this compound using data from the available draft report. Bromodichloromethane caused statistically significant increases in tumors of several types and sites in F344/N rats and B6C3F1 mice (see Section 4.2. and Tables 4-1 and 4-2). Calculations performed with

TABLE 6-1

Cancer Data Sheet for Derivation of q_1^* for Chlorodibromomethane

Compound: chlorodibromomethane

Reference: NTP, 1985

Species/strain/sex: mice, B6C3F1, female

Route/vehicle: gavage, corn oil

Length of experiment (le) = 105 weeks

Length of study (Le) = 105 weeks

Lifespan of animal (L) = 105 weeks

Body weight = 0.035 kg (estimated from growth curves)

Tumor type and site: hepatocellular adenomas or carcinomas

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0 mg/kg, 5 days/week	0	6/50
50 mg/kg, 5 days/week	35.71	10/49
100 mg/kg, 5 days/week	71.43	19/50

Unadjusted q_1^* from study = 6.7×10^{-3} $(mg/kg/day)^{-1}$

Human q_1^* = 8.4×10^{-2} $(mg/kg/day)^{-1}$

TABLE 6-2

Cancer Data Sheet for Derivation of q_1^* for Bromodichloromethane

Compound: bromodichloromethane

Reference: NTP, 1986a

Species/strain/sex: mice, B6C3F1, female

Route/vehicle: gavage, corn oil

Length of experiment (le) = 102 weeks

Length of study (Le) = 102 weeks

Lifespan of animal (L) = 102 weeks

Body weight = (estimated from growth curves)

Tumor type and site: hepatocellular adenomas or carcinomas

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
0 mg/kg, 5 days/week (bw = 0.038 kg)	0	3/50
75 mg/kg, 5 days/week (bw = 0.035 kg)	4.25	18/48
150 mg/kg, 5 days/week (bw = 0.030 kg)	8.08	29/50

Human $q_1^* = 1.3 \times 10^{-1}$ $(mg/kg/day)^{-1}$

these data indicated that the largest estimate of carcinogenic potency (q_1^*) would be obtained using the data for combined incidence of hepatocellular adenomas or carcinomas in female mice. Incidences of these tumors were significantly higher than controls (3/50) for both low-dose (18/48) and high-dose (29/50) female mice ($p<0.001$, Fischer exact test). The dose-related trend was also statistically significant ($p<0.001$, Cochran-Armitage trend test). Data used in the calculation of the q_1^* are presented in Table 6-2. Because the body weights of the female mice were affected by treatment, dosages were corrected for body weight [i.e., multiplied by $(W_a/70)^{1/3}$] before entering data into the model. Using the GLOBAL 82 multistage model (Howe and Crump, 1982), a human q_1^* of 1.3×10^{-1} $(mg/kg/day)^{-1}$ was calculated.

6.3.2. Inhalation. Inhalation data for the three trihalomethanes were insufficient for quantitative carcinogenicity risk assessments.

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APPENDIX A

Summary Table for Bromodichloromethane in Female B6C3F1 Mice*

Experimental Exposure/Dose	Effect	q_1^*
0,75,150 mg/kg/day 5 days/week for 102 weeks; gavage in corn oil	increased combined incidences of hepatocellular adenoma or carcinoma	1.3×10^{-1} $(mg/kg/day)^{-1}$

*Source: NTP, 1986a

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APPENDIX B

Summary Table for Bromoform

Route	Species	Experimental Exposure/Dose	Effect	Reference Dose (mg/day)*	Reference
Oral					
RfD_{90} (formerly AIS)	rat	50 ppm in drinking water for 90 days (5.6 mg/kg/day)	increased incidence and intensity of liver lesions at higher doses	4.0	Chu et al., 1982; U.S. EPA, 1982
RfD_0 (formerly AIC)	rat	50 ppm in drinking water for 90 days (5.6 mg/kg/day)	increased incidence and intensity of liver lesions at higher doses	0.4	Chu et al., 1982; U.S. EPA, 1982
Maximum					
CS	mice	12.5 mg/kg/day (RV_d=4.3)	suppression of hepatic phagocytosis (RV_e=6)	RV_d = 4.3 CS = 25.8	Munson et al., 1978; U.S. EPA, 1983b

*RfD_S and RfD values are calculated as mg/day for a 70 kg reference human

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APPENDIX C

Summary Table for Chlorodibromomethane in Female B6C3F1 Mice*

Experimental Exposure/Dose	Effect	q_1^*
0, 50, 100 mg/kg/day, 5 days/week for 105 weeks; gavage in corn oil	increased combined incidences of hepatocellular adenoma or carcinoma	8.4×10^{-2} $(mg/kg/day)^{-1}$

*Source: NTP, 1985